No. 3

A NEW SYNTHESIS OF 4(OR 5)-β-AMINOETHYL-GLYOXALINE, ONE OF THE ACTIVE PRINCIPLES OF ERGOT.

BY

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LXXIV.—*A New Synthesis of 4(or 5-)-β-Aminoethylglyoxaline, one of the Active Principles of Ergot.*

By Frank Lee Pyman.

Barger and Dale (Trans., 1910, **97**, 2592) have recently shown that 4(or 5)-β-aminoethylglyoxaline (β-iminazolylethylamine) occurs in certain aqueous extracts of ergot, and Dale and Laidlaw (*J. Physiol.*, 1910, **41**, 318) have shown that its physiological activity is very great.

This base was first prepared by Windaus and Vogt (*Ber.*, 1907, **40**, 3691), who synthesised it from glyoxaline-4(or 5)-propionic acid through the hydrazide, azide, and urethane by Curtius's method. Glyoxaline-4(or 5)-propionic acid is obtained synthetically only in poor yield by the action of formaldehyde and ammonia on glyoxylpropionic acid (Knoop and Windaus, *Beitr. chem. Physiol. Path.*, 1905, **7**, 144), but may more readily be prepared from the naturally occurring amino-acid histidine (*l*-α-amino-β-glyoxaline-4(or 5)-propionic acid); the latter is, however, a somewhat expensive compound, and 4(or 5)-β-aminoethylglyoxaline is, therefore, not readily accessible by this method.

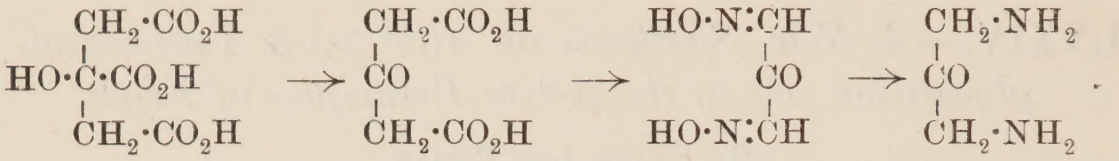
Recently, this base has been prepared directly from histidine by the elimination of carbon dioxide, both by bacterial action (Ackermann, *Zeitsch. physiol. Chem.*, 1910, **65**, 504), and by chemical methods (Ewins and Pyman, this vol., p. 339).

No other method for the preparation of the base has hitherto been described, and its production has, therefore, practically depended on a supply of the naturally occurring amino-acid histidine.

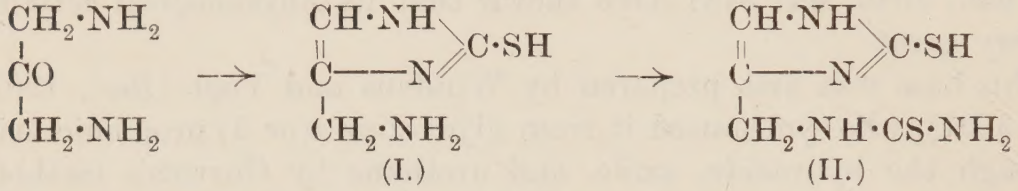
In view of the possible therapeutic importance of this base, it seemed, therefore, important to devise some method by which it could conveniently be synthesised from readily available material, and the following method was found to be suitable. The method is based on Gabriel's discovery (*Ber.*, 1893, **26**, 2204; 1894, **27**, 1037) that amino-ketones of the general formula $R{\cdot}CO{\cdot}CH_2{\cdot}NH_2$ yield, on condensation with potassium thiocyanate, thiolglyoxalines of the general formula $R{\cdot}C\overset{CH{\cdot}NH}{\underset{\|}{}}\!\!>\!C{\cdot}SH$, which may be oxidised by nitric acid to glyoxalines of the type $R{\cdot}C\overset{CH{\cdot}NH}{\underset{\|}{}}\!\!>\!CH$.

Diaminoacetone dihydrochloride formed the starting material for this synthesis, and this compound is readily prepared from citric acid, through acetonedicarboxylic acid and di*iso*nitrosoacetone by

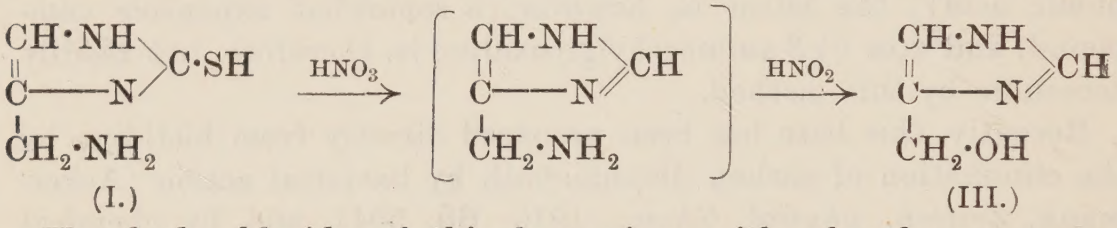
Kalischer's method (*Ber.*, 1895, **28**, 1519), the course of the reaction being shown by the following scheme:



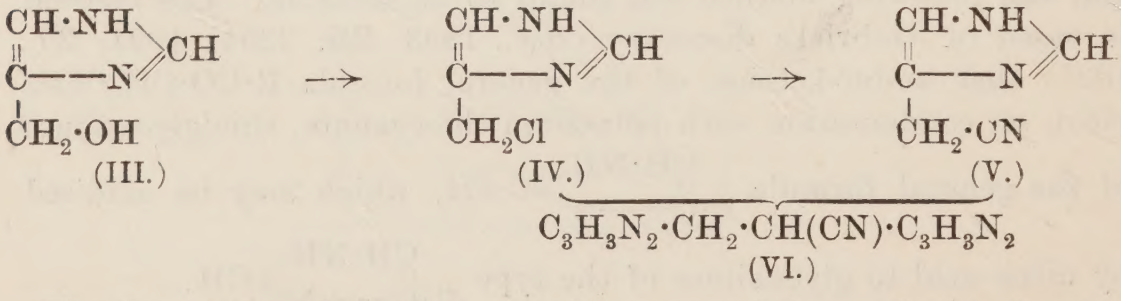
Diaminoacetone dihydrochloride, when heated with one molecular proportion of potassium thiocyanate, readily yields 2-*thiol*-4(or 5)-*aminomethylglyoxaline* (I), together with small quantities of 2-*thiol*-4(or 5)-*thiocarbamidomethylglyoxaline* (II):



On oxidising the former compound with nitric acid, the thiol sulphur is removed as sulphuric acid, and a glyoxaline results, as in Gabriel's experiments, but the free nitrous acid formed in the reaction attacks the amino-group, replacing it by a hydroxyl group, and the resulting product is 4(or 5)-*hydroxymethylglyoxaline* (III):



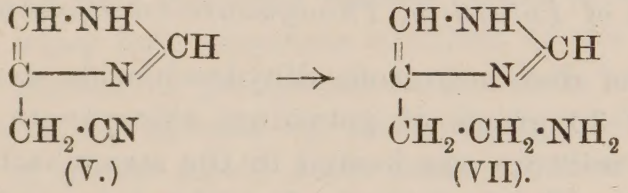
The hydrochloride of this base gives with phosphorus pentachloride an excellent yield of the hydrochloride of 4(or 5)-*chloromethylglyoxaline* (IV), and this salt, when dissolved in alcohol and dropped into an ice-cold, saturated aqueous solution of potassium cyanide, gives a 50 per cent. yield of 4(or 5)-*cyanomethylglyoxaline* (V). The latter base, however, is accompanied by a quantity of *αβ-bis*[4(or 5)-*glyoxaline*]-*propionitrile* (VI), besides a considerable quantity of oily by-products, which have not yet been further examined:



The formation of the last-named compound is, no doubt, due to the condensation of a molecule of the cyano-compound with a molecule of the chloro-compound; it is analogous to the formation

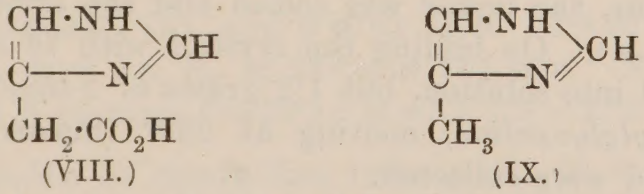
of αβ-bis(*o*-nitrophenyl)propionitrile when *o*-nitrobenzyl chloride and potassium cyanide are boiled together for several hours in aqueous alcoholic solution (Bamberger, *Ber.*, 1886, **19**, 2635). The conditions under which the latter reaction takes place are, of course, more severe, and it may be pointed out that in the preparation of phenylacetonitrile from benzyl chloride and potassium cyanide prolonged boiling in aqueous alcoholic solution is also necessary. The extraordinary reactivity of 4(or 5)-chloromethylglyoxaline, indicated by the ease with which the halogen is replaced, emphasises the marked influence of the glyoxaline complex on the side-chain. An attempt was made to effect the replacement of the chloro- by the cyano-group in absolute alcoholic solution, but after several hours' boiling of the hydrochloride of the chloro-compound with finely powdered potassium cyanide in this solvent, a complex mixture was obtained, from which a certain amount of 4(or 5)-*ethoxymethylglyoxaline*, $C_3H_3N_2 \cdot CH_2 \cdot OEt$, but none of the cyano-compound, could be isolated.

The last stage of the synthesis of 4(or 5)-β-aminoethylglyoxaline (VII) was accomplished by the reduction of 4(or 5)-cyanomethylglyoxaline by means of sodium and alcohol:



(V.) (VII).

when there were also obtained as by-products a large amount of glyoxaline-4(or 5)-acetic acid (VIII) and a small quantity of 4(or 5)-methylglyoxaline (IX):



(VIII.) (IX.)

Glyoxaline-4(or 5)-acetic acid, which is thus prepared synthetically for the first time, has previously been obtained by Knoop (*Beitr. chem. Physiol. Path.*, 1907, **10**, 119) by the oxidation of oxydeaminohistidine (α-hydroxy-β-glyoxaline-4(or 5)-propionic acid). It has now been further characterised by the preparation of a number of salts, and its ester, *ethyl glyoxaline*-4(or 5)-*acetate*, has been prepared by the action of alcoholic hydrogen chloride on 4(or 5)-cyanomethylglyoxaline.

The occurrence of 4(or 5)-methylglyoxaline amongst the reduction products of 4(or 5)-cyanomethylglyoxaline is probably due to the loss of carbon dioxide on the part of glyoxaline-4(or 5)-acetic acid.

It was thought possible that the yield of 4(or 5)-β-aminoethylglyoxaline might be increased by converting the cyano-compound into the corresponding thioamide, and reducing this with zinc and dilute hydrochloric acid, a method advantageously employed by Hofmann (*Ber.*, 1868, **1**, 102), and subsequently by Bamberger and Lodter (*Ber.*, 1888, **21**, 51) in the formation of bases of the type $R{\cdot}CH_2{\cdot}NH_2$ from cyanides R·CN, where R is an aryl radicle; in the present case, however, whilst *glyoxaline*-4(or 5)-*acetthioamide*, $C_3H_3N_2{\cdot}CH_2{\cdot}CS{\cdot}NH_2$, was formed almost quantitatively from 4(or 5)-cyanomethylglyoxaline and alcoholic ammonium sulphide, its reduction led to mere traces of the required product.

In conclusion, it may be mentioned that several of the new glyoxaline derivatives described in this communication form suitable starting points for the synthesis of more complicated substances containing the glyoxaline ring, and it is proposed to attempt the synthesis of such compounds, in particular of those which occur in nature, namely, histidine and pilocarpine.

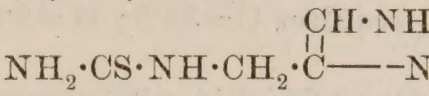
Experimental.

The Action of Potassium Thiocyanate on Diaminoacetone.

Fifty grams of diaminoacetone dihydrochloride were added to a hot solution of 30 grams of potassium thiocyanate in 50 c.c. of water, and the mixture was heated in the steam-bath. At first, a clear solution was obtained, but after about ten minutes crystals began to separate. After heating for about one hour, no further quantity of crystals appeared to be formed, and after heating for another half-hour, the liquor was cooled and the crystals collected (mother liquor *M*). On boiling the crystals with 75 c.c. of water, the bulk passed into solution, but 1·2 grams of 2-*thiol*-4(or 5)-*thiocarbamidomethylglyoxaline*, melting at 233° (uncorr.), remained undissolved, and were collected.

The filtrate was then mixed with a solution of 21 grams of anhydrous potassium carbonate in 75 c.c. of water, somewhat evaporated, and set aside, when 8·2 grams of 2-*thiol*-4(or 5)-*aminomethylglyoxaline*, melting at 188°, separated. To the mother liquor from this crop of crystals the mother liquor *M* was added, and the mixture evaporated to dryness under diminished pressure and extracted with alcohol. After removing the solvent from the alcoholic extract and diluting the resulting dark brown oil with a little water, further crops of nearly pure 2-thiol-4(or 5)-aminomethylglyoxaline, amounting to 17·9 grams, were obtained. The total yield of this base—26·1 grams—represents 64 per cent. of the theoretical.

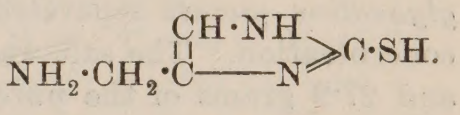
2-*Thiol*-4(or 5)-*thiocarbamidomethylglyoxaline*,



This compound crystallises from boiling water in small, transparent, isolated prisms, which melt and decompose at 237—238° (corr.). It is anhydrous, and is very sparingly soluble in boiling water or alcohol. It is insoluble in dilute hydrochloric acid, but soluble in aqueous sodium hydroxide:

0·1533 gave 0·1807 CO_2 and 0·0607 H_2O. C = 32·1; H = 4·4.
$C_5H_8N_4S_2$ requires C = 31·9; H = 4·3 per cent.

2-*Thiol*-4(or 5)-*aminomethylglyoxaline*,



This base crystallises from water or alcohol in large, clear, colourless, quadrilateral plates, which melt and decompose at 188° (corr.). It is anhydrous, and is moderately easily soluble in cold water, sparingly so in cold absolute alcohol, but very easily so in hot water. It is sparingly or very sparingly soluble in the other usual organic solvents, even when hot. Aqueous solutions of the base yield with silver nitrate solution a precipitate in the form of a fine, yellow powder, which is not affected by ammonia, but becomes white on the addition of dilute nitric acid; such solutions give a white, amorphous precipitate with aqueous mercuric chloride or a solution of zinc hydroxide in ammonia, and an intense red coloration on the addition of sodium diazobenzene-*p*-sulphonate:

0·1538 gave 0·2079 CO_2 and 0·0783 H_2O. C = 36·9; H = 5·7.
0·0744 „ 20·6 c.c. N_2 at 21° and 764 mm. N = 32·3.
$C_4H_7N_3S$ requires C = 37·2; H = 5·5; N = 32·5 per cent.

The *hydrochloride* crystallises from water in crusts formed by rosettes of needles. This salt darkens at 265°, and is quite charred at 270° (corr.), when it shrinks somewhat, but does not melt. It is anhydrous, and easily soluble in cold water, giving a solution neutral to litmus:

0·1531 gave 0·1647 CO_2 and 0·0685 H_2O. C = 29·3; H = 5·0.
0·1615 „ 0·1737 CO_2 „ 0·0735 H_2O. C = 29·3; H = 5·1.
$C_4H_7N_3S$,HCl requires C = 29·0; H = 4·9 per cent.

The *picrate* crystallises from water in large, stout, serrated needles of an intense orange colour, which decompose at 237° (corr.). This salt is anhydrous, and is fairly easily soluble in hot water, but very sparingly so in cold:

0·1541 gave 0·1898 CO_2 and 0·0438 H_2O. C = 33·6; H = 3·2.
0·1526 „ 0·1873 CO_2 „ 0·0445 H_2O. C = 33·5; H = 3·2.
$C_4H_7N_3S,C_6H_3O_7N_3$ requires C = 33·5; H = 2·8 per cent.

The Action of Nitric Acid on 2-Thiol-4(or 5)-aminomethylglyoxaline.

Fifteen grams of 2-thiol-4(or 5)-aminomethylglyoxaline were added gradually during twenty minutes to 300 c.c. of 10 per cent. aqueous nitric acid, which was kept gently boiling over a small flame. The clear, pale yellow liquor was then boiled for ten minutes, neutralised with aqueous sodium hydroxide, and mixed with a solution of 26·6 grams of picric acid in 600 c.c. of boiling water. On cooling, a large quantity of 4(or 5)-*hydroxymethylglyoxaline picrate* separated, and further crops were obtained on concentration. The salt was purified by crystallisation from water, and 27·9 grams of the pure picrate were obtained; the yield thus amounted to 74 per cent. of the theoretical.

4(or 5)-*Hydroxymethylglyoxaline*, $HO\cdot CH_2\cdot C\begin{matrix}CH\cdot NH\\ \|\\ N\end{matrix}\!\!>CH$.

This base may be obtained from its picrate by shaking the latter with dilute hydrochloric acid and ether until the picric acid is removed, adding to the resulting solution of the hydrochloride an excess of sodium carbonate, evaporating to dryness under diminished pressure, and extracting with absolute alcohol. It crystallises from absolute alcohol in large, clear, colourless hexahedra, which melt at 93—94° (corr.). It is very easily soluble in water, easily so in absolute alcohol, but sparingly so in the other usual organic solvents. It cannot be distilled under 20 mm. pressure, but suffers decomposition:

0·1519 gave 0·2717 CO_2 and 0·0844 H_2O. C = 48·8; H = 6·2.
0·1010 „ 24·6 c.c. N_2 at 22° and 767 mm. N = 28·4.
$C_4H_6ON_2$ requires C = 49·0; H = 6·2; N = 28·6 per cent.

Aqueous solutions of this base give with mercuric chloride, ammoniacal silver nitrate, and ammoniacal solution of zinc hydroxide, white, amorphous precipitates; with sodium diazobenzene-*p*-sulphonate, an intense red coloration.

The *hydrochloride* crystallises from absolute alcohol in long, flat, prismatic needles, which melt at 107—109° (corr.), after sintering from 105°. It is very deliquescent, and very easily soluble in water or alcohol:

0·1542* gave 0·2019 CO_2 and 0·0778 H_2O. C = 35·7; H = 5·7.
0·1383* „ 0·1820 CO_2 „ 0·0702 H_2O. C = 35·9; H = 5·7.

* Dried at 100°.

0·0855* gave 15·3 c.c. N_2 at 18° and 751 mm. N = 20·7.
0·1587* „ 0·1700 AgCl. Cl = 26·5.

$C_4H_6ON_2,HCl$ requires C = 35·7; H = 5·3; N = 20·9; Cl = 26·3 per cent.

The *nitrate* crystallises from absolute alcohol in wedge-shaped, transparent plates, which melt at 84—86° (corr.), after sintering a few degrees earlier. It is deliquescent, very easily soluble in water or hot absolute alcohol, and easily so in cold absolute alcohol:

0·1399* gave 0·1526 CO_2 and 0·0580 H_2O. C = 29·7; H = 4·6.

$C_4H_6ON_2,HNO_3$ requires C = 29·8; H = 4·3 per cent.

The *picrate* crystallises from water in glistening scales, which melt and decompose at 207° (corr.). It is anhydrous, and is fairly easily soluble in hot water, but very sparingly so in cold:

0·1388 gave 0·1862 CO_2 and 0·0401 H_2O. C = 36·6; H = 3·2.

$C_4H_6ON_2,C_6H_3O_7N_3$ requires C = 36·7; H = 2·8 per cent.

The *hydrogen oxalate* crystallises from water in large, clear, colourless prisms, which contain one molecule of water of crystallisation, and have no sharp melting point, commencing to sinter at 80°, and gradually liquefying between this temperature and 100°. After drying, first at about 50°, then at 100°, this salt melts at 134—136° (corr.). It is soluble in about four parts of cold water, and very easily soluble in hot water:

0·1500† gave 0·1906 CO_2 and 0·0662 H_2O. C = 34·7; H = 4·9.
0·2118† lost 0·0182 at 100°. H_2O = 8·6.

$C_4H_6ON_2,C_2H_2O_4,H_2O$ requires C = 34·9; H = 4·9; H_2O = 8·7

0·1488* gave 0·2072 CO_2 and 0·0545 H_2O. C = 38·0; H = 4·1.

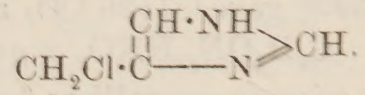
$C_4H_6ON_2,C_2H_2O_4$ requires C = 38·3; H = 4·3 per cent.

The Action of Phosphorus Pentachloride on 4(or 5)-*Hydroxymethylglyoxaline.*

To 57 grams of phosphorus pentachloride contained in a round-bottomed flask, 36·5 grams of 4(or 5)-hydroxymethylglyoxaline hydrochloride were added in small portions, with thorough shaking, in the course of a few minutes. Copious fumes of hydrogen chloride were evolved, and the reaction mass quickly became a viscous liquid, and then solidified. Fifty c.c. of chloroform were then added, to wash any unchanged pentachloride into contact with unchanged hydroxy-compound, and the mixture was then heated on the water-bath, first under ordinary, and then under diminished, pressure to remove chloroform, hydrogen chloride, and phosphoryl chloride. The residue was then dissolved in about

* Dried at 100°. † Air dried salt.

50 c.c. of hot absolute alcohol, and set aside, when 33·0 grams of 4(or 5)-*chloromethylglyoxaline hydrochloride*, melting at 140—142°, separated; on allowing the mother liquor to evaporate spontaneously in a desiccator, a further 2·8 grams of the same salt, in a fairly pure condition, were obtained. The total yield—35·8 grams—amounts to 86 per cent. of the theoretical, and further quantities were obtained by again treating the residual oil with phosphorus pentachloride.

4(or 5)-*Chloromethylglyoxaline*, 

The *hydrochloride* crystallises from absolute alcohol in prismatic needles or stout prisms, which melt at 144—145° (corr.). This salt is deliquescent, very easily soluble in water or hot absolute alcohol, and fairly easily so in cold absolute alcohol:

0·1531* gave 0·1750 CO_2 and 0·0558 H_2O. C = 31·2; H = 4·1.

0·1539* „ 0·2866 AgCl. Cl = 46·1.

$C_4H_5N_2Cl,HCl$ requires C = 31·4; H = 4·0; Cl = 46·3 per cent.

Aqueous solutions of this salt remain clear on the addition of aqueous sodium carbonate, but become turbid, depositing a yellow oil soluble in excess, on the addition of aqueous sodium hydroxide.

The *picrate* is obtained in long, glistening, silky yellow needles, when a cold solution of picric acid is added to a freshly prepared solution of 4(or 5)-chloromethylglyoxaline hydrochloride in cold water. It is anhydrous, and melts and decomposes at 181° (corr.):

0·1434 gave 0·1810 CO_2 and 0·0334 H_2O. C = 34·4; H = 2·6.

$C_4H_5N_2Cl,C_6H_3O_7N_3$ requires C = 34·7; H = 2·3 per cent.

On dissolving this salt in a little boiling water, and immediately cooling the solution, pure 4(or 5)-hydroxymethylglyoxaline picrate, melting at 207° (corr.), either alone or when mixed with the pure salt, separates.

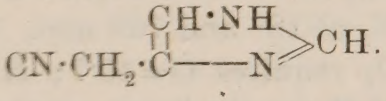
The Action of Aqueous Potassium Cyanide on 4(or 5)-*Chloromethylglyoxaline.*

A solution of 30 grams of 4(or 5)-chloromethylglyoxaline hydrochloride in 135 c.c. of absolute alcohol was added drop by drop to 90 grams of potassium cyanide in 100 c.c. of water, which was mechanically stirred and kept at about 0°, the addition occupying approximately thirty minutes. The mixture was then filtered, and the potassium salts washed with alcohol. The filtrate and washings were combined, mixed with 180 c.c. of 10 per cent. aqueous sodium

* Dried at 100°.

carbonate, and evaporated to dryness under diminished pressure. The residue was extracted with warm ethyl acetate, and the extract distilled, when 16·3 grams of a brown oil remained. This began to crystallise, and after dissolution in a little warm water, 7·5 grams of pure 4(or 5)-*cyanomethylglyoxaline* separated, and a second crop of 1·0 gram of the cyano-base was obtained on concentrating the mother liquor. The oily liquor remaining was then converted into the acid oxalate by the addition of 9 grams of oxalic acid, and the resulting crops of mixed oxalates fractionally crystallised from water, when small quantities of 4(or 5)-cyanomethylglyoxaline acid oxalate and *αβ-bis*[4(or 5)-*glyoxaline*]-*propionitrile hydrogen oxalate* were obtained. These oxalates, however, readily crystallise out side by side, and their separation is tedious. The total yield of 4(or 5)-cyanomethylglyoxaline amounts to about 50 per cent. of the theoretical.

4(or 5)-*Cyanomethylglyoxaline*,



This base crystallises from water or ethyl acetate in stout, prismatic needles, which sinter at 136°, soften at 137°, and melt to a clear liquid at 138—140° (corr.). It is sparingly soluble in ether, chloroform, benzene, light petroleum, or cold water, but easily so in ethyl acetate, acetone, alcohol, or hot water:

0·1339 gave 0·2755 CO_2 and 0·0573 H_2O. C = 56·1; H = 4·8.
0·0673 „ 22·5 c.c. N_2 at 19° and 770 mm. N = 39·6.
$C_5H_5N_3$ requires C = 56·0; H = 4·7; N = 39·2 per cent.

Aqueous solutions of this base give with mercuric chloride, ammoniacal silver nitrate, and ammoniacal solution of zinc hydroxide, white, amorphous precipitates; with sodium diazobenzene-*p*-sulphonate, a dirty brownish-red colour, very much more intense than the beautiful red colour given by other glyoxalines containing a free imino-hydrogen atom, is produced; the difference is probably due to the product containing two chromophoric groups, one of which is attached to the imino-group as in other glyoxalines, and the second to the methylene group which is situated between the glyoxaline complex and the cyano-group.

The *hydrochloride* crystallises from absolute alcohol in thin, glistening leaflets, which melt at 168—169° (corr.). It is very easily soluble in water, and fairly easily so in boiling absolute alcohol, but sparingly so in the latter when cold:

0·1514 gave 0·2315 CO_2 and 0·0585 H_2O. C = 41·7; H = 4·3.
$C_5H_5N_3$,HCl requires C = 41·8; H = 4·2 per cent.

The *hydrogen oxalate* crystallises from water in crusts consisting of indefinite prisms. This salt decomposes at 194° (corr.), and is easily soluble in hot water, but sparingly so in cold:

0·1542 gave 0·2403 CO_2 and 0·0546 H_2O. C = 42·5; H = 4·0.

$C_5H_5N_3,C_2H_2O_4$ requires C = 42·6; H = 3·6 per cent.

The *picrate* crystallises from water in yellow leaflets, which begin to sinter at 155°, and melt at 165—166° (corr.). It is sparingly soluble in cold water or alcohol.

αβ-Bis[4(or 5)-*Glyoxaline*]-*propionitrile*,
$C_3H_3N_2{\cdot}CH_2{\cdot}CH(CN){\cdot}C_3H_3N_2$.

The *hydrogen oxalate* crystallises from water in stout, clear, prismatic needles, which melt and decompose at 181—182° (corr.). It is anhydrous and somewhat sparingly soluble in cold water, but easily so in hot water:

0·1528 gave 0·2288 CO_2 and 0·0477 H_2O. C = 40·8; H = 3·5.

0·1052 „ 15·2 c.c. N_2 at 18° and 769 mm. N = 17·2.

$(C_9H_{10}N_5)_2,5C_2H_2O_4$ requires C = 40·7; H = 3·7; N = 17·0; $C_2H_2O_4$ = 54·5 per cent.

On dissolving 2·05 grams of this salt in water, and adding an excess of barium hydroxide solution, 2·8 grams of barium oxalate, corresponding with 54·6 per cent. of oxalic acid were collected; the filtrate from this, after treatment with carbon dioxide and removal of barium carbonate, was evaporated to dryness, when a colourless varnish remained. This was readily soluble in water, giving an alkaline solution, and when acidified with hydriodic acid and evaporated to low bulk, gave a beautifully crystalline hydriodide.

The *hydriodide* crystallises from water in well-formed rhombic prisms, which melt at 200—201° (corr.). It is sparingly soluble in cold water or alcohol, and is anhydrous:

0·1539 gave 0·1932 CO_2 and 0·0467 H_2O. C = 34·2; H = 3·4.

0·1472 „ 27·4 c.c. N_2 at 14° and 768 mm. N = 22·4.

0·2030 „ 0·1496 AgI. I = 39·8.

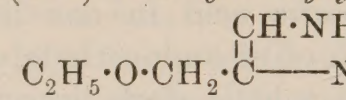
$C_9H_{10}N_5,HI$ requires C = 34·2; H = 3·5; N = 22·2; I = 40·1 per cent.

The Action of Alcoholic Potassium Cyanide on 4(or 5)-*Chloromethylglyoxaline.*

Ten grams of 4(or 5)-chloromethylglyoxaline hydrochloride, 12 grams of finely powdered potassium cyanide, and 40 c.c. of absolute alcohol were boiled together under a reflux condenser for five and a-half hours. The mixture was then filtered from the potassium salts, and these washed with alcohol; the filtrate was rendered

alkaline with 80 c.c. of 10 per cent. aqueous sodium carbonate, and evaporated to dryness under diminished pressure. The residue was thoroughly extracted with ether, and gave 5·6 grams of pale yellow oil; this was mixed with its own weight of oxalic acid, and the acid oxalates fractionally crystallised from water, when 3·4 grams of pure 4(or 5)-*ethoxymethylglyoxaline hydrogen oxalate* were obtained; besides this oxalate, which separates first in large crystals, other crystalline oxalates were present in the mother liquors. No 4(or 5)-cyanomethylglyoxaline hydrogen oxalate could be isolated from them by fractional crystallisation, and they were not further examined.

4(or 5)-*Ethoxymethylglyoxaline*,



This base is liberated from the oxalate by treating the latter with baryta, filtering from barium oxalate, and removing the excess of baryta as carbonate. It crystallises from anhydrous ether in prismatic needles, which sinter from 50°, and melt at 53—55° (corr.).

It is easily soluble in water, and the usual organic solvents, with the exception of light petroleum:

0·1530 gave 0·3219 CO_2 and 0·1097 H_2O. C = 57·4; H = 8·0.
0·1533 „ 0·3199 CO_2 „ 0·1094 H_2O. C = 56·9; H = 8·0.
$C_6H_{10}ON_2$ requires C = 57·1; H = 8·0 per cent.

The *hydrogen oxalate* crystallises from water in large prisms, which melt at 165—167° (corr.). It is anhydrous, and is soluble in about 4 parts of cold water, but readily so in hot water:

0·1563 gave 0·2668 CO_2 and 0·0839 H_2O. C = 46·6; H = 6·0.
0·1443 „ 0·2457 CO_2 „ 0·0794 H_2O. C = 46·4; H = 6·2.
0·1274 „ 16·0 c.c. N_2 at 21° and 754 mm. N = 14·5.
$(C_6H_{10}ON_2)_4,(C_2H_2O_4)_3$ requires C = 46·5; H = 6·0; N = 14·6 per cent.

The Reduction of 4(or 5)-*Cyanomethylglyoxaline. Preparation of* 4(or 5)-*β-Aminoethylglyoxaline.*

Ten grams of 4(or 5)-cyanomethylglyoxaline were dissolved in 50 c.c. of absolute alcohol, and 25 grams of sodium added piece by piece within a few minutes. Further quantities of hot absolute alcohol were added a few c.c. at a time, while the mixture was heated by a small flame, until after the addition of about 200 c.c. of absolute alcohol (making 250 c.c. in all) in the course of an hour and a-quarter, nearly all the sodium had dissolved. A little

water was then added to remove the last traces of sodium, and the liquor was acidified by the addition of 120 c.c. of concentrated hydrochloric acid. After removing the sodium chloride, and washing this with alcohol, the filtrate was evaporated to low bulk, mixed with 100 c.c. of cold saturated aqueous sodium carbonate, and evaporated to complete dryness under diminished pressure. The residue was then extracted with absolute alcohol, which removed all the organic matter, and the extract was concentrated to about 50 c.c., when, on cooling, 4·65 grams of crude *sodium glyoxaline-4(or 5)-acetate* were deposited as a crystalline powder, which was collected, washed with absolute alcohol, and reserved. The alcoholic mother liquor left on evaporation about 8 grams of a viscid brown oil. This was dissolved in a little water, and added to a boiling solution of 30 grams of picric acid in one litre of water. On cooling, a quantity of 4(or 5)-β-aminoethylglyoxaline dipicrate crystallised out, mixed with a little dark brown resinous matter; after recrystallisation from water, the latter was removed, and 14·6 grams of pure dipicrate were obtained.

4(or 5)-β-Aminoethylglyoxaline dipicrate, either alone or mixed with the salt prepared from histidine (Ewins and Pyman, *loc. cit.*), melted and decomposed at 238—242° (corr.), according to the rate of heating:

0·1487 gave 0·1946 CO_2 and 0·0375 H_2O. C = 35·7; H = 2·8.
$C_5H_9N_3,(C_6H_3O_7N_3)_2$ requires C = 35·8; H = 2·7 per cent.

It was further identified by converting it into the dihydrobromide which melted and decomposed at 284° (corr.):

0·1541 gave 0·1232 CO_2 and 0·0578 H_2O. C = 21·8; H = 4·2.
$C_5H_9N_3,2HBr$ requires C = 22·0; H = 4·1 per cent.

Dr. P. P. Laidlaw, of the Wellcome Physiological Research Laboratories, kindly tested a specimen of this synthetic 4(or 5)-β-aminoethylglyoxaline dipicrate, and found that it had the physiological activity of the pure salt prepared from histidine.

After the separation of the dipicrate, the mother liquors deposited first a crystalline picrate, melting at about 160—170°, and then a sticky oil; these fractions, on extraction with a little warm alcohol, gave 0·6 gram of 4(or 5)-β-aminoethylglyoxaline dipicrate as a sparingly soluble residue. This was collected, and all the picrate mother liquors—alcoholic and aqueous—were then combined and boiled to remove the alcohol. The clear hot solution was mixed with concentrated hydrochloric acid, cooled, filtered from picric acid, and extracted with ether to remove the remainder of the latter. The resulting solution of hydrochlorides was made alkaline with sodium carbonate, evaporated to complete dryness

under diminished pressure, and extracted first with ether, then with absolute alcohol.

From the ethereal extract, 1·0 gram of nearly colourless, viscid oil was obtained. This was converted into the picrate, and crystallised first from water, then from alcohol, when 1·35 grams of pure 4(or 5)-methylglyoxaline picrate were isolated. This salt melted at 160—162° (corr.), both alone and when mixed with the salt prepared from the pure base; the latter salt had the same melting point. Windaus and Knoop (*Ber.*, 1905, **38**, 1170) give 159—160°:

0·1471 gave 0·2074 CO_2 and 0·0397 H_2O. C = 38·5; H = 3·0.

0·1028 „ 19·4 c.c. N_2 at 13° and 775 mm. N = 23·0.

$C_4H_6N_2,C_6H_3O_7N_3$ requires C = 38·6; H = 2·9; N = 22·5 per cent.

The alcoholic extract left, on evaporation, 1·2 grams of crude crystalline sodium 4(or 5)-glyoxaline acetate; this was combined with the 4·65 grams which had separated earlier, neutralised with hydrochloric acid, and converted into the picrate, when 11·5 grams of pure glyoxaline-4(or 5)-acetic acid picrate, melting at 212—213° (corr.), were obtained. The yield of 4(or 5)-β-aminoethylglyoxaline —15·2 grams of the dipicrate—amounts to 29 per cent., and that of glyoxaline-4(or 5)-acetic acid to 35 per cent., of the theoretical.

Glyoxaline-4(or 5)-*acetic Acid*, $C_3H_3N_2{\cdot}CH_2{\cdot}CO_2H$.

This substance was obtained by treating its hydrochloride with silver carbonate, filtering from silver chloride, removing the excess of silver present as glyoxalineacetate by means of hydrogen sulphide, and concentrating the liquor to low bulk, when it separated in fan-shaped clusters of prismatic needles, which melt and decompose at 222° (corr.):

0·1613 lost 0·0201 at 100°. H_2O = 12·5.

$C_5H_6O_2N_2,H_2O$ requires H_2O = 12·5 per cent.

0·1412 gave 0·2466 CO_2 and 0·0600 H_2O. C = 47·6; H = 4·8.

$C_5H_6O_2N_2$ requires C = 47·6; H = 4·8 per cent.

This acid has previously been prepared by Knoop (*Beitr. chem. Physiol. Path.*, 1907, **10**, 111) by the oxidation of oxydeamino-histidine, that is, α-hydroxy-β-glyoxaline-4(or 5)-propionic acid, $C_3H_3N_2{\cdot}CH_2{\cdot}CH(OH){\cdot}CO_2H$. He describes it as fan-shaped needles from aqueous acetone, which contain $1H_2O$, and melt and decompose at 220°.

The *hydrochloride* crystallises from absolute alcohol in small needles, which melt and decompose at 225—226° (corr.), after sintering a few degrees earlier. It is anhydrous, and is very easily soluble in water, but sparingly so in alcohol:

0·1541 gave 0·2080 CO_2 and 0·0618 H_2O. C = 36·8; H = 4·5.
0·2002 „ 0·1767 AgCl. Cl = 21·8.
$C_5H_6O_2N_2$,HCl requires C = 36·9; H = 4·4; Cl = 21·8 per cent.

The *picrate* crystallises from hot water in handsome yellow plates, which melt at 212—213° (corr.). It is anhydrous and easily soluble in hot water or alcohol, but sparingly so in these solvents when cold:

0·1515 gave 0·2044 CO_2 and 0·0371 H_2O. C = 36·8; H = 2·7.
0·0830 „ 13·5 c.c. N_2 at 13° and 773 mm. N = 19·7.
$C_5H_6O_2N_2$,$C_6H_3O_7N_3$ requires C = 37·2; H = 2·6; N = 19·8 per cent.

Sodium glyoxaline-4(or 5)-acetate crystallises from absolute alcohol in small needles containing half a molecular proportion of water of crystallisation, which is retained at 100°, but lost at 120°. This salt is very easily soluble in water, and fairly easily so in hot absolute alcohol:

0·1633 * lost 0·0087 at 120°. H_2O = 5·3.
0·2144 * gave 0·0955 Na_2SO_4. Na = 14·4.
$C_5H_5O_2N_2Na,\frac{1}{2}H_2O$ requires Na = 14·6; H_2O = 5·8 per cent.
0·1546 † gave 0·0724 Na_2SO_4. Na = 15·2.
$C_5H_5O_2N_2Na$ requires Na = 15·5 per cent.

Ethyl Glyoxaline-4(or 5)-acetate, $C_3H_3N_2 \cdot CH_2 \cdot CO_2Et$.

Five grams of 4(or 5)-cyanomethylglyoxaline were dissolved in 25 c.c. of absolute alcohol, and a stream of dry hydrogen chloride passed through the solution while boiling gently. After two or three minutes, ammonium chloride began to separate out, and after ten minutes, this was removed by filtration. The liquor was evaporated almost to dryness under diminished pressure, and the sticky residue dissolved in about 30 c.c. of hot acetone, when, on cooling, crude ethyl glyoxaline-4(or 5)-acetate hydrochloride separated. After recrystallisation from acetone, 4·2 grams of this salt were obtained in a pure state, and the mother liquors contained more of this salt mixed with glyoxaline-4(or 5)-acetic acid hydrochloride.

Ethyl glyoxaline-4(or 5)-acetate hydrochloride crystallises from acetone in clusters of prismatic needles, which melt at 115—117° (corr.). It is deliquescent, very easily soluble in water or alcohol, fairly easily soluble in hot, but sparingly so in cold, acetone:

0·1538 * gave 0·2471 CO_2 and 0·0803 H_2O. C = 43·8; H = 5·9.
$C_7H_{10}O_2N_2$,HCl requires C = 44·1; H = 5·8 per cent.

The free base may be isolated as a colourless oil by mixing the

* Dried at 100°. † Dried at 120°.

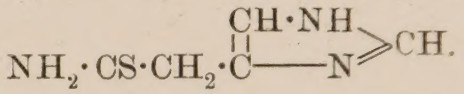
hydrochloride with a slight excess of 10 per cent. aqueous sodium carbonate, evaporating to dryness in a vacuum, and extracting with ethyl acetate.

The *hydrogen oxalate* crystallises from water in large prisms, which melt and decompose at 180° (corr.), after sintering a few degrees earlier. It is anhydrous, and is easily soluble in water, but sparingly so in alcohol:

0·1503 gave 0·2443 CO_2 and 0·0665 H_2O. C = 44·3; H = 5·0.

$C_7H_{10}O_2N_2,C_2H_2O_4$ requires C = 44·2; H = 5·0 per cent.

Glyoxaline-4(or 5)-*acet-thioamide*,



Three grams of 4(or 5)-cyanomethylglyoxaline were dissolved in 30 c.c. of alcohol, mixed with 30 c.c. of a cold saturated alcoholic solution of ammonium sulphide, and kept overnight at 40° in a closed vessel. On distilling off the greater part of the alcohol under diminished pressure, the thio-derivative crystallised from the residual liquor while still warm, and 2·5 grams of the pure substance in the form of a nearly white, crystalline powder were obtained in the first crop, and further small quantities subsequently.

Glyoxaline-4(or 5)-*acet-thioamide* crystallises well from water in prisms, and from absolute alcohol in rosettes of needles. On heating, it darkens slightly from about 140°, and considerably from 160°, and eventually melts and decomposes at 173° (corr.). It is easily soluble in hot water, fairly easily so in hot absolute alcohol, and sparingly so in these solvents when cold. It is anhydrous:

0·1543 gave 0·2419 CO_2 and 0·0703 H_2O. C = 42·8; H = 5·1.

$C_5H_7N_3S$ requires C = 42·5; H = 5·0 per cent.

On reducing 1 gram of this base with zinc dust and dilute hydrochloric acid in cold alcoholic solution for several days, and working up the reaction product for 4(or 5)-β-aminoethylglyoxaline, only about 0·05 gram of the dipicrate of this base was obtained.

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